

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT



Proving the eDiary Dividend

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For all the promises of the impact of technology on clinical trials—from enhanced trial efficiencies to reduced time to market—very few specific examples have been published that clearly demonstrate a marked impact. This article provides just such an example, by examining the impact of electronic diaries (eDiaries) on the collection of Patient Reported Outcome (PRO) data in a large, pivotal Phase III trial evaluating a medication for the treatment of overactive bladder (OAB). We compare the results obtained using eDiaries to capture real-time data on voluntary and involuntary micturitions with those obtained from a Phase II trial that used paper diaries. The result: measurable subject protocol compliance and significantly reduced error variance, yielding increased study sensitivity and the opportunity to realize a significant financial savings in future trials.

The eDiary was used to assess the efficacy of a medication for overactive bladder. Subjects were provided with an eDiary and asked to record all micturitions at the time of occurrence (up to 30 times per day in some subjects) for a period of 14 weeks. In contrast, an earlier study asked subjects to record micturitions on paper diaries three times daily during a similar

eDiary data can reduce recall bias and enhance the sensitivity of PRO data, paying off in reduced error variance and significant financial savings in future clinical trials.

treatment period. Subjects in the current eDiary protocol made self-initiated entries for 91% of their micturitions over the course of the day, thereby substantially reducing any data bias that could have resulted from subjects trying to recall their micturition data after-the-fact. The impact of this real-time entry on the data was a substantial reduction in error, or noise, in the pri-

mary endpoint (micturitions per day), compared to the previous paper diary trial. Specifically, the study's data variability was reduced by 33%. This reduction in error variance translates into a substantial increase in the trial's statistical power, from 80% (expected based on paper diary performance) to 98% (actual power based on eDiary performance). The reduced noise and increased power translates into more efficient clinical research. It is anticipated that future OAB eDiary trials can be conducted with up to 50% fewer subjects, resulting in 45% lower costs per trial.

The high compliance with the real-time protocol minimized recall bias, and the eDiary trial yielded data of much higher quality and integrity than the earlier paper diary trial. The remainder of this article discusses how this reduction in variability was achieved with science-based methods deployed using Palm and Web technology and the implications of these findings for other eDiary trials.

Real-time patient-reported outcomes

Patient-reported outcome data are used to evaluate the efficacy and/or safety of a drug in approximately 75% of all Phase II–IV

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clinical trials. While many types of PRO data can be adequately captured at the investigative site (e.g., global Quality of Life measurements), some PRO data are based upon subjects' day-to-day experience (e.g., number of micturitions or daily pain). For this latter type of data, subjects in approximately 25% of all clinical trials are asked to carry diaries and complete them on a daily or moment-by-moment basis.¹

In the area of overactive bladder specifically, subject diaries have long been used as the primary indicator of treatment efficacy.² The promise of these diaries is data that is more proximal to medical events (or moments) and therefore more accurate than data based on recall, potentially eliminating the biases that influence and skew recall-based data. There is well-documented evidence demonstrating that recall of biographical information is not a straightforward retrieval of events.^{3,4} Memory relies on a variety of mental shortcuts, or heuristic strategies, to reconstruct past events. This retrospective reconstruction is imperfect and vulnerable to a range of biases. These biases, in turn, can affect the sensitivity of the clinical trial.⁵ Thus, diary protocols calling for frequent data entry are used primarily in order to obtain data that is not plagued by such recall biases.

To the extent that diaries realize this promise, the result can be data of high quality and integrity that can be relied upon by pharmaceutical companies and regulatory bodies to make decisions regarding the safety and efficacy of drugs, biologics, and medical devices.

Scientific quality and integrity data standards are captured in the statistical concepts of reliability and validity. Reliable data arise when a trial implements a measurement instrument that yields as little error variance as possible. This means that the variability in a subject's data is due to the disease and treatment and not due to problems with measurement. Validity refers to implementation of a study design and to measures that accurately evaluate the phenomenon of interest; the trial really measured what it set out to measure. Validity is limited by reliability: a measure that is unreliable cannot be valid.

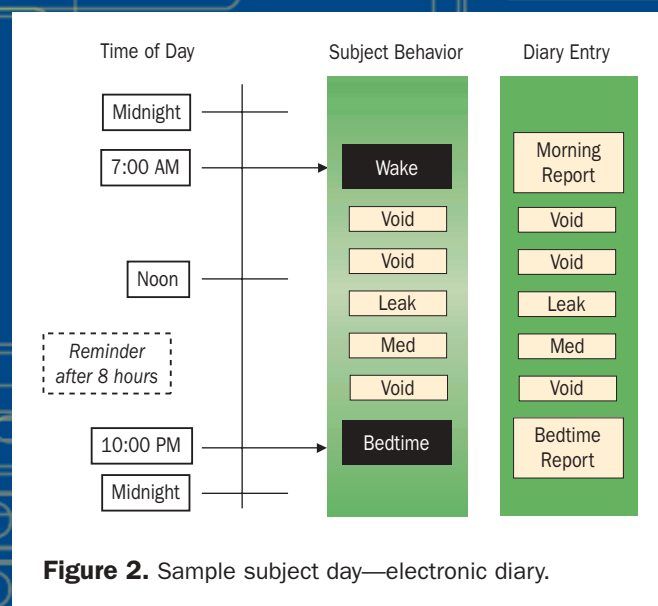
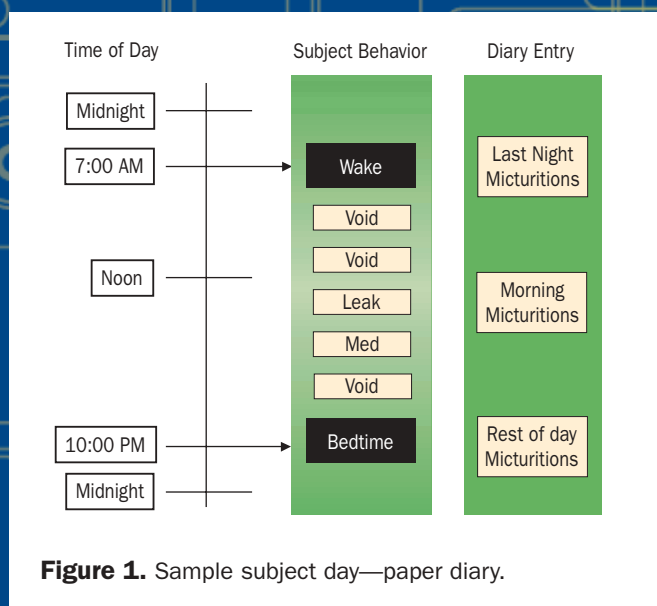
While many factors can impact the reliability and validity of data, in diary trials untimely completion of the diary itself is one of the key sources of error or unreliability. As stated above, if subjects complete diaries long after the fact, the data are susceptible to the same recall biases that diaries attempt to avoid. These recall biases in turn introduce noise or unreliability. Data

Paper vs. eDiaries: Comparing Compliance

A study recently published in the *British Medical Journal* addressed compliance with paper diaries and electronic diary methods. Dr. Arthur Stone and his colleagues⁶ conducted a study that directly assessed subjects' compliance with a diary protocol implemented using both paper and electronic diary methods. Subject compliance was assessed using a newly developed instrumented paper diary that electronically tracked diary use unobtrusively. Compliance rates from this instrumented paper diary (IPD) were compared with those achieved using a state-of-the-art eDiary. The primary objective of the study was to quantify compliance with paper diaries.

The apparent compliance in the IPD group was very high: subjects submitted paper diary cards corresponding to an average of 90% of assessment occasions. This is consistent with the existing literature on reported compliance with paper diaries. The objective record told a different story, however: actual compliance was much lower, averaging only 11% (95% CI: 8%–14%). Thus, 89% of paper diary cards were falsified. The pattern of noncompliance was informative. On 32% of study days, the IPD had not been opened at all, so subjects had neglected their task for the entire day. However, subjects submitted 94% of the required cards for those days. These compliance findings show that subjects were very noncompliant with the protocol when using paper diaries. Further, it demonstrated that compliance is often faked by subjects using paper diaries, giving the false impression of good compliance.

In contrast, the eDiary achieved an actual compliance rate of 94% (95% CI: 91%–96%). These high rates of subject compliance are consistent with findings from several peer-reviewed studies using a compliance-enhancing electronic diary system.⁶



captured after-the-fact could also be invalid if subjects are simply unable to accurately recall events.

Data reliability is also affected by the number of recorded measurements. The more measurements a subject completes, the higher the reliability, because multiple assessments “triangulate” on the real value. However, if subjects are completing the diaries after-the-fact, functionally entering many medical moments at the same time, the potential benefit of multiple measurements will not be realized.

In other words, completion of diaries after-the-fact and in batches can undermine the reliability and validity of diary data. Empirical studies suggest that these problems occur often. In a recent study published in the *British Medical Journal*, Arthur Stone and colleagues⁶ demonstrated that subjects’ compliance with timely completion of paper diaries is only 11%—in other words, 89% of paper diaries are not completed according to the protocol (see sidebar for study details). In the area of OAB specifically, studies have consistently found that subjects are not compliant with their paper-voiding diaries.^{7–9} One study found that only 32% of subjects record details of their symptoms in their paper diaries.¹⁰ Compliance with paper diaries also appears to decline over time in OAB studies. In fact, research has shown test periods longer than 72 hours are associated with increased rates of noncompliance.¹¹ The impact of this noncompliance is the introduction of recall biases and reduced scientific quality and integrity of the data.

In exploring alternatives to paper diaries, clinical researchers have looked to eDiary solutions. A growing body of evidence supports the assertion that subject compliance and resulting data quality can be increased with eDiary systems. For example, Stone *et al.*⁶ achieved actual compliance of 94% (95% CI: 91%–96%) in an eDiary arm of the trial (see sidebar). These high rates of subject compliance are consistent with findings from multiple peer-reviewed studies using a compliance-enhancing eDi-

ary system.^{6, 12–14} The implication of this high level of compliance is that the data are not influenced by recall bias and are of higher quality and integrity.

A Phase III trial using eDiaries

This article evaluates the impact of subject compliance with a real-time protocol on scientific quality and integrity. The results from a Phase III pivotal trial of an OAB medication conducted using eDiary methods are compared to the results of an earlier paper-voiding diary trial.

In the eDiary study, approximately 800 subjects who met criteria for OAB at 80 investigative sites were randomized. Consistent with the epidemiology of OAB, the study sample was 90% female, with an average age of 57 years (range 18 to 93 years).

The primary objective of this Phase III trial was to compare the frequency of daily micturitions both voluntary and involuntary (leaks) in active treatment vs. placebo groups over a 12-week treatment period. A two-week pretreatment period with placebo served as the baseline for comparison of treatment effects. In order to optimally capture these events, subjects were asked to carry the eDiaries with them on a daily basis and enter their data in real-time, immediately after the micturition.

Previous paper diary trial. The results summarized here for the Phase III trial are contrasted to a previous Phase II paper diary

Table 1. Study results—error variance

| Change Baseline to Avg. Per Day | Effect Size* | Predicted Pooled Std. Dev.† | Actual Pooled Std. Dev. | Predicted vs. Actual (% reduction) |
|---------------------------------------|-----------------|-----------------------------------|-------------------------------|--|
| Incont. Episodes | 0.7 | 2.55 | 1.71 | 33% |
| Voluntary Voids | 0.9 | 3.30 | 2.30 | 30% |

* Estimated treatment effect

† Estimated from earlier paper-voiding study

trial. In that study, approximately 650 subjects with similar inclusion/exclusion criteria were randomized to a 12-week period. Subjects were asked to complete diaries three times per day, reporting their voluntary and involuntary micturitions for the period between the last and current report (see Figure 1).

Procedures. The goal of the Phase III trial was to obtain the highest quality data possible in order to accurately assess the drug effect. One way to achieve this was through implementation of an eDiary methodology, with the aim of eliminating recall bias. In contrast to the previous paper diary trial, a real-time design was implemented where subjects were asked to enter information into an eDiary throughout the day, as micturitions occurred (see Figure 2).

eDiary use in the field. Subjects used the eDiaries for 14 weeks: two weeks for baseline characterization and 12 weeks for active or placebo treatment. Prior to using the eDiaries, subjects were thoroughly trained by investigative staff using a combination of hands-on experience with the eDiary together with verbal and written instructions.

The daily experience with the eDiary was similar for each day and is depicted in Figure 2. Subjects “woke up” the eDiary when they awoke for the day and reported micturitions that had occurred during the night. They entered micturitions throughout the day and finally they put the eDiary to “sleep” at night. Nighttime micturitions could still be entered in real-time if subjects so chose. The subjects placed the eDiary into a modem/cradle combination after putting it to sleep. The eDiary device automatically dialed and transferred the data to a central data server via a secure Internet transmission. The study management team used a Web-based subject performance tracking system to allow trial staff to monitor subject compliance and, where appropriate, give compliance feedback to subjects. The overall process is depicted in Figure 3.

A number of compliance features were included in the eDiary system. Compliance is partially achieved by ensuring that the system fits naturally into the subjects’ day-to-day life. To that end, features included a napping function that allowed subjects to rest during the day and a sleep function that allowed subjects to set their own wake times. Compliance was also achieved by designing very simple user interfaces. To enter a micturition, subjects simply turned on the eDiary, selected the type of micturition, and answered four questions, after which the device turned itself off. The entire process took only a few seconds. Finally, compliance on the eDiary is achieved by monitoring and responding to potential periods of noncompliance. For example, during daytime hours, if subjects did not make an entry into the system for an eight-hour period during the day, the eDiary emitted an audible alarm and queried the subject about missing any micturition events. At the end of each day, when putting the eDiary to “sleep” for the night, subjects were asked to retrospectively enter any micturitions not entered during the day. During the course of the night, subjects could enter micturitions on the eDiary, but a report completed each morning also asked about nighttime micturitions. In these ways, the system was designed to assure protocol compliance.

eDiary design, development, and validation. A central aspect of the eDiary system was that it was designed, developed, and validated to U.S. Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH) standards for systems collecting electronic data (for details of the validation process, see prior article in *Applied Clinical Trials*¹⁵), as well as the software development industry’s best practices. The process began by developing specification documents for the system based upon the clinical protocol and meetings with the clinical study team and the technical team. The task of developing the specifications required a combination of scientific collaboration on the clinical study design and application of human behavioral principles to specify an eDiary system that would drive subject compliance to the diary protocol.

Following formal approval of the specifications, the software was configured (using an eDiary scripting tool) and tested. The technical team first tested the completed system to confirm the basic functionality of the system. Next, the sponsor conducted user acceptance testing with volunteers similar to the actual

If challenges are identified, they can be circumvented. If they are not, they can be responsible for curtailing an entire clinical development program.

subjects for the trial. This latter (“beta”) testing demonstrated that the system functioned as specified with people in a clinical trial setting. Most important, the beta subjects reported positively on the usability of the system.

Concurrent with the configuration of the software, training materials were prepared for all users, including subjects, investigative site staff, and clinical monitors. The investigative staff and clinical monitors were certified to use the system and train subjects. Following this preparation and testing of the training materials, the system was deployed in the trial.

Results & discussion

Reported here are the results of the study that evaluate the impact of this eDiary methodology on the data quality and integrity. The first set of analyses evaluated subjects’ compliance with the real-time monitoring. A second set of analyses compared the data in this trial to the previous trial that used paper diaries.

Protocol compliance. The intent to treat (ITT) population was used to ensure no potential sample selection bias. The following standard approach was adopted for the purposes of examining protocol compliance¹⁶: (number of real-time events during the

subject's waking day, divided by total daily events during the day) X 100. The numerator was the number of micturition events entered during the course of each day (see Figure 2). The denominator was the combination of the daily micturition entries, plus those micturitions entered in the end-of-day report given at bedtime or following an eight-hour reminder. The average compliance rate for the entire 14 weeks with the eDiaries was 91% (SD \pm 13%). Moreover, subjects maintained relatively consistent performance over the entire study period (see Figure 4), with baseline compliance of 94% (SD \pm 11%) and end of treatment compliance of 87% (SD \pm 20%). An even more stringent compliance metric was also computed; only those micturition entries reported within 30 minutes of the event were counted as compliant. Over the entire 14-week monitored period, an average of 85% (SD \pm 16%) of all daytime micturitions were entered within 30 minutes of their occurrence.

The frequency of reminders was also analyzed. Again, these occurred when subjects had not entered any micturitions for

eight hours during the day. On average, only 6% (SD \pm 9%) of all micturitions were entered via these reminders.

One of the most surprising findings was compliance with nighttime micturition entries. Subjects were given the option to enter micturitions into the eDiary at night if they woke up to void after putting the eDiary to sleep, or they could wait until the morning. It was anticipated that over 80% of these nighttime entries would be recorded the next morning. However, on average, fully 43% (SD \pm 39%) of all nighttime micturitions were entered in real-time during the course of the night. This suggests the degree of subject engagement that the eDiary inspired and adds to the validity of the data.

One commonly voiced concern is the ability of elderly patients to use an eDiary system. To assess this, we divided the sample into those older or younger than 65 and examined compliance on both groups. There was a trend for subjects over 65 years, who represented 30% of the sample, to do somewhat better than the younger study subjects. For example, subjects over 65 reported an average of 94% micturitions in real-time, as compared to 90% for those under 65 years. The older subjects in the sample also reported more nighttime micturitions in real-time: 48% vs. 42%. This trend remained consistent on all of the other compliance metrics as well. These data support the contention that a well-designed eDiary system can be used by older patient populations.⁵

Study power. The very high compliance rates in this study were expected to impact other measures of data quality. The results of this Phase III trial were compared to the earlier Phase II study conducted with paper diaries.

While the mean micturition values were similar between the two trials, there was a substantial difference in the variability of the diary-recorded outcome variable in the two trials. The error variance estimates are shown in Table 1. The actual error variance in the eDiary trial was 33% lower than that in the paper diary trial.

Increased study sensitivity and statistical power is the benefit of reduced variability. This translates into a better chance to demonstrate efficacy and reduced sample size. Using the higher variability from the paper diary trial, it had been estimated that the study would have 80% power—that is, an 80% chance of detecting a clinically meaningful effect of the drug. Because the eDiary data were less variable, in fact the trial had a 98% chance of detecting these same effects. Going forward, new trials can be planned with updated sample size estimates based on the eDiary's performance. The 33% reduction in variance translates into roughly a 50% reduction in the number of subjects needed to statistically demonstrate efficacy. It is esti-

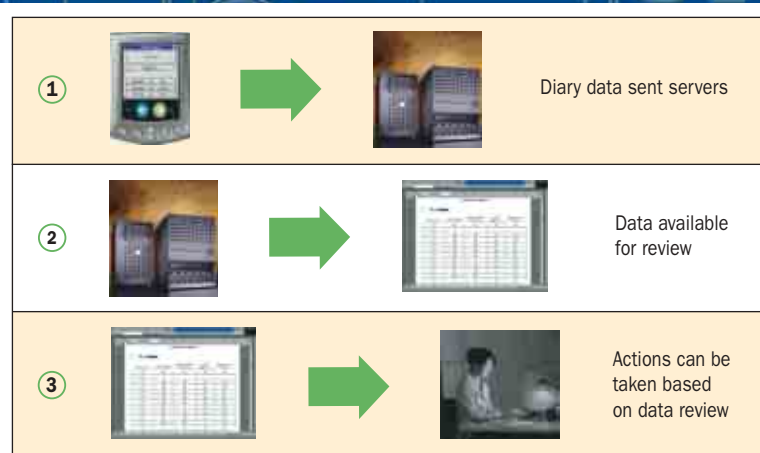


Figure 3. System overview.

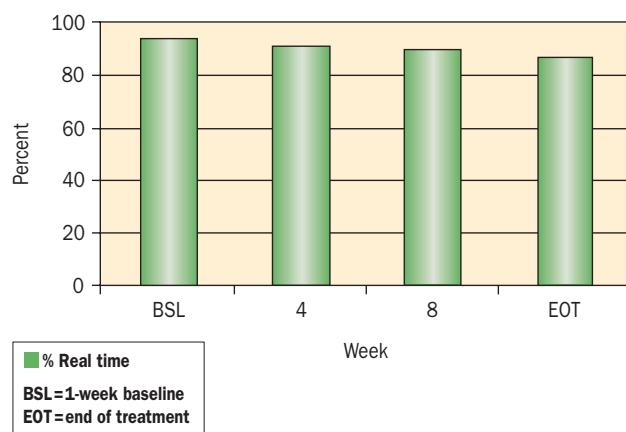


Figure 4. Weekly real-time entry.

mated that this could reduce trial costs by 45% and trial duration by 60%.

Conclusions

This study clearly demonstrates that relative to paper diaries, eDiaries can improve the scientific quality and integrity of PRO data. At a minimum, the eDiary, unlike paper diaries, allows for an evaluation of subjects' compliance with the protocol. That is, automatic time-stamping in the eDiary, along with a variety of other compliance-enhancing features, can be used to evaluate and remediate when necessary to improve subject compliance. In contrast, prior paper methods do not allow for this compliance evaluation or remediation. In virtually all studies that implement paper diaries (with the exception of the instrumented paper study⁷ by Stone and colleagues), the only measure of compliance is the submission of the diary card. But this offers no assurance that the diary was completed at the protocol-dictated time. Thus, an important advance with eDiaries is simply the ability to evaluate on a daily basis (if so desired) whether the protocol is being followed.

The ability to evaluate subjects' compliance is, of course, only the first step. The real goal is not just to assess compliance with the diary protocol, but to achieve high compliance, thereby minimizing recall bias that can obscure treatment effects. This trial clearly reached that goal. Subjects reported being extremely compliant with timely completion of the eDiary. In fact, subjects were unexpectedly compliant during the nighttime hours, where retrospective recording was anticipated. Finally, this high compliance occurred across the full age range of the

It may be compliance not just with any protocol but an appropriate protocol that is also important in obtaining reduction in variability.

subjects, with older subjects doing slightly better using the eDiaries to record their micturations. It should be noted the compliance measures reported here were based upon subjects' reports. There is no way to "objectively"

determine if the subjects' reports accurately reflect the actual physiological occurrences of micturations. This notwithstanding, the convergence of multiple compliance measures points to high levels of data integrity.

The high rates of compliance observed are not unique to this trial. Shiffman and colleagues have conducted a number of eDiary trials, averaging approximately 90% compliance rates across trials.⁶ Further, the compliance results in this trial are consistent with OAB subjects' reports of preference for electronic diaries in other trials. In studies with OAB subjects,¹⁷⁻¹⁹ subjects have expressed a clear preference for electronic

Table 2. Summary of ALCOA and compliance by paper and electronic subject diary data

| Quality component | Definition | Paper Diary Compliance | Electronic Diary Compliance |
|-------------------|--|---|---|
| Attributable | Data should be attributable to a specific subject. | The attributability of a paper-based diary is typically determined through the subject's handwriting. | The attributability of eDiary source data is established by a subject password, which is required every time an entry is made into the system, and is private and unique to the subject. |
| Legible | Data should be legible for purposes of recording and interpretation. | If the data are not legible, they are functionally missing if the subject is unable to clarify at the time of investigator review. | The legibility of the eDiary source data is not an issue since the data is captured in an electronic format that can be unambiguously reported. |
| Contemporaneous | Data should be contemporaneous to the event it is intended to record. | Establishing that paper diary data is contemporaneous is difficult or impossible because it is not possible to verify the timely completion of the diary cards. | Time and date stamping allow evaluation of timely completion. eDiary systems lock subjects out of making entries beyond a certain point in time, ensuring that the data are entered timely (or, if not entered timely, the data will be missing). |
| Original | Data must be recorded such that the original information is not obscured in any way. | This can be accomplished by reviewing the diary pages to ensure that no undocumented changes have been made. | Originality is maintained by not allowing subjects to change data once it has been committed to the database on the eDiary unit. |
| Accurate | Data should accurately reflect the subject's experience. | Given the difficulty in establishing that paper diary cards were completed in a timely fashion, it is unclear how to determine the data's accuracy. | Time-stamped entries and audit trails support accuracy of the data. |

diaries over paper diaries. For example, one study asked 36 women with bladder symptomatology and 36 women without symptoms (ranging in age from 20 to 84 years) to use an electronic and a traditional paper diary in a crossover design to record their voiding, urgency, leakage, and fluid intake. Among patients with a bladder condition, fully 100% preferred the electronic diaries.¹⁷

There are many possible reasons for the high rates of subject compliance found in this and other eDiary trials. In a recent review of trials using eDiaries, Hufford and Shields⁵ extracted a number of principles that also appear to be related to high levels of protocol compliance. The first is the eDiary vendor's experience using eDiaries; the eDiary vendor used in this trial has developed and implemented eDiaries for over 15 years. Second, the inclusion of features that enhance the system's "livability" leads to greater compliance. This study incorporated a number of features (such as an alarm clock) that made the system accommodating of the subjects' lifestyle (as opposed to forcing a change in the subjects' daily activity flow). Finally, proper training is related to achieving high rates of compliance.^{20,21} In the current trial, investigative staff were thoroughly trained on how to train subjects, and as a result each subject received standardized training. Taken together, these factors may have significantly contributed to the subjects' compliance in this trial.

Reducing variability

One important consequence of subject compliance is the reduced variability found in this trial. Another contributor to reduced variability may be the study design itself. In the previous paper diary trial, subjects retrospectively entered their micturitions three times per day. In contrast, the subjects in the current trial entered each micturition as it occurred, which averaged 13 events in a 24-hour period. As discussed earlier, the greater the number of measurements recorded, the higher the reliability (or lower the variability). This scientific approach to capturing data real-time, maximizing the number of measurements from subjects, is based upon a set of principles developed by Saul Shiffman and Arthur Stone called Ecological Momentary Assessment.²² Thus, it may not simply be compliance with any protocol, but compliance with an appropriate protocol that focuses on capturing the most accurate reflection of the subject's experience that is also important in obtaining reduction in variability.

The result of reduced variability is high scientific quality and integrity of the data. In any clinical trial, the study design and the methods employed aim to reduce the amount of error in measuring the safety and/or efficacy of the drug's effects. In this trial, subject compliance with the protocol minimized recall bias, which in turn decreased measurement error. Additionally, the study design maximized the number of measures taken from subjects. There was an overall increase in the reliability (because of reduced error variance) and the validity of the data captured (based upon the apparent decrease in recall bias) in the trial, providing a more accurate reflection of a drug

effect. This is evidenced by the 33% reduction in variance. In turn, this increased the probability of detecting a treatment effect (if there was one to detect) from 80% to 98%. In the simplest terms, this provided a very high level of confidence that the results were not attributable to mere chance.

The protocol compliance achieved in this trial also provides strong support for the regulatory quality and integrity of the data. The FDA's primary criteria for data quality and integrity are often referred to as ALCOA; data must be attributable, legible, contemporaneous, original, and accurate (see Table 2).²³ Subjects' reports of timely entry of 91% of all micturitions clearly supports that the data in this trial were contemporaneous. The concomitant reduction in error variance supports the accuracy of the data. Finally, the design and validation of the system ensured that the data were attributable to a specific subject, legible, and that the original data were not obscured or altered in any manner.

While the impact on scientific and regulatory integrity of the data are the most important consequences of protocol compliance, the reduction of error variance also has practical benefits to pharmaceutical development. Future efficacy trials with this population of OAB subjects can be conducted using sample sizes that are approximately 50% lower. In the world of increasing expense and challenge in drug development, this is a substantial gain. Further, smaller sample sizes reduces the exposure of subjects to investigational drug compounds.

The results of this study clearly demonstrate how a new research tool, eDiaries, resulting from a combination of a behavioral science and robust technology, can have significant impact on the data quality and integrity, as well as on drug development economics and timelines.

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